REMARKS

Claims 2 – 20 are currently pending in the application. Claims 2 – 4 and 6 - 16 have been withdrawn from consideration as being drawn to a non-elected invention. Claim 1 has been cancelled. Claim 5 has been amended. New claims 17 – 20 have been added. No new matter has been added, support for the new claims and the amendments being found throughout the specification and the claims as filed.

Claim Rejections 35 U.S.C. §112, written description

Claims 1 and 5 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Claim 1 has been cancelled making this rejection now moot. Applicants respectfully traverse the rejection of claim 5.

The Examiner argues that "the rejected claims provides no structural limitation regarding what is encompassed by the terms 'polymorphism at base number position 3932 of the aplipoprotein E gene,' 'polymorphism at the base number position –863 of the tumor necrosis factor alpha gene,' or 'polymorphism at base number position 825 of G-protein beta3 subunit gene." (Office Action, p.4). Applicants respectfully disagree. The instant claims now define the base number position of the polymorphism as it relates to the position in the corresponding SEQ ID. For example, Applicants recite in claim 5 a "polymorphism at the **base number position -863 (the 197th base of SEQ ID NO:3)** of the human tumor necrosis factor-α gene." (emphasis added). Thus, Applicants clearly provide structural limitation regarding the position of the base in relation to the corresponding sequence.

The Examiner further argues that "the instant invention encompasses a method comprising the analysis of an enormous and wide variety of nucleic acid sequences." (Office Action, p.4). The Examiner argues that "(t)he specification teaches SEQ ID NOs: 1, 3 and 4, which are sequences corresponding to the human genes that contain the claimed

polymorphisms, however the specification does not further define the sequences for any other organism...(and) the specification does not provide guidance on the meaning of 'nucleic acid sample' and, therefore, said sample and said polymorphisms could be from any organism." (Office Action, p.4). Further, the Examiner argues that "the specification provides only sequences of the human polymorphisms (and) ...does not provide any characteristics that would allow one to identify any other homologous genes and polymorphisms from another organism or any particular portions or fragments or variants of the disclosed sequence that would allow for the genotyping of said polymorphisms or further for characterizing those genotypes with restenosis." (Office Action, p.4 – 5). Applicants respectfully disagree.

The instant claims now define the method for diagnosing the risk of restenosis after coronary angioplasty in a **human** subject, analyzing the polymorphisms (1), (3) and (4) in a **human** nucleic acid sample, where the polymorphisms are in a **human** gene. Accordingly, the instant method identifies human polymorphisms and not polymorphisms from another organism.

In view thereof, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

Claim Rejections 35 U.S.C. §112, enablement

Claim 5 was rejected under 35 U.S.C. § 112 first paragraph for allegedly failing to comply with the enablement requirement. Applicants respectfully traverse the rejection.

The Examiner has considered the following *In re Wands* factors in the rejection (*In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404):

The breadth of the claims and the nature of the invention

According to the MPEP at 2164. 05(a), "whether the specification would have been enabling as of the filing date involves consideration of the nature of the invention, the state of the prior art, and the level of skill in the art. The initial inquiry is into the nature of the

invention, i.e., the subject matter to which the claimed invention pertains. The nature of the invention becomes the backdrop to determine the state of the art and the level of skill possessed by one skilled in the art."

As to the nature of the invention, the Examiner alleges that "the rejected claim encompasses analysis of any nucleic acid sample from any organism for the elected polymorphisms." (Office Action, p.8). The Examiner argues that "the nature of the invention not only involves determining the genotype of the elected polymorphisms but also correlating those genotypes with a risk for restenosis in all organisms." (Office Action, p.9).

Instant claim 5 is drawn to a method for diagnosing the risk of restenosis after coronary angioplasty in a human subject, analyzing the polymorphisms (1), (3) and (4) in a human nucleic acid sample, where the polymorphisms are in a human gene. The specification provides Examples teaching how the gene polymorphisms were selected and determined (Examples 1 and 2, respectively) and provides Examples that teach association of the polymorphism with restenosis after coronary angioplasty and the development of a method for diagnosing restenosis after coronary angioplasty (Example 3) by correlating the genotypes of the elected polymorphisms with a risk for restenosis. Accordingly, the nature of the invention is enabled as claimed.

The amount of guidance and working examples

According to the MPEP at 2164.02, "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." Moreover, "an applicant need not have actually reduced the invention to practice prior to filing. In Gould v. Quigg, 822 F.2d 1074, 1078, 3 USPQ 2d 1302, 1304 (Fed. Cir. 1987). The Court held that "the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it." 822 F.2d at 1078, 3 USPQ2d at 1304 (quoting In re Chilowsky, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956)). "The specification need not contain an example if the

invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. In re Borkowski, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)."

The Examiner indicates that "the specification teaches the sequences of the elected polymorphisms for the human genes and provides SEQ ID NOs 1, 2 and 4 to identify the human genes and polymorphisms in those genes." (Office Action, p.9). The Examiner argues that "the specification provides data that demonstrates an odds ratio of 7.33 as a predictor of risk of restenosis in Japanese men when the patient has a defined polymorphism in each gene. However the specification does not provide information on how the odds ratio was determined." (Office Action, p.9). Applicants respectfully disagree.

The specification provides ample teaching and examples as to how the odds ratios (relative risk) were determined. Applicants direct the Examiner, for example, to paragraph [0351] of the published application, which teaches the statistical methodology used to determine odds ratios:

> The present inventors performed the stepwise forward selection method of multivariate logistic regression analysis (FIGS. 10 and 11). In this method, either a dominant or recessive model was used based on the P values (lower P values) for association of each polymorphism with restenosis after coronary angioplasty shown in FIGS. 8 and 9...**Odds ratios restenosis after balloon dilatation or stent implantation based on combined genotypes with the stepwise forward selection method** is shown in FIGS. 12, 13 and 16A for men and in FIGS. 14, 15 and 16B for women. (emphasis added)

Stepwise forward selection is a method of statistical analysis known by one of skill in the art and is routinely used in regression analysis of data. Accordingly, Applicants have provided teaching as to the statistical analysis used to determine p-values, and thus the p-values have correlation to the identified polymorphisms in restenosis.

The Examiner argues further that "in women, polymorphisms at the base number

position 3932 of the aplipoprotein E gene and at the base number position –863 of the tumor necrosis factor-alpha gene were examined relative to their role in correlating with a risk for restenosis, however the polymorphism at the base number position 825 of G-protein beta3 subunit gene was not examined for its role in restenosis in women." (Office Action, p.10).

Applicants provide examples that the combination of the (1), (3) and (4) polymorphisms, corresponding to polymorphisms in the human aplipoprotein E gene, human tumor necrosis factor-α gene and human G-protein β3 subunit gene, respectively, are associated with restenosis after coronary angioplasty. Applicants direct the Examiner to Example 3, which teaches selection of polymorphisms associated with restenosis after coronary angioplasty and development of methods for diagnosing restenosis after coronary angioplasty, and specifically teaches the (1), (3) and (4) polymorphisms. Applicants teach at paragraph [0172] of the specification that the combination of polymorphisms (1), (3) and (4) is preferred:

> In the case where detection is carried out by combining five or less of polymorphisms, it is preferable to preferentially select the polymorphisms with higher odds ratios as in Examples mentioned below... **(I)n the case where three polymorphisms are used in combination, it is preferable to select (1), (3) and (4)**.

Moreover, Applicants teach at paragraph [0354] that the G-protein β3 subunit gene may be important in the etiology of restenosis, and provide references that support this idea (see, e.g. Circulation 1997;96:1299-304.; Iaccarino G. Smithwick L A, Lefkowitz R J, Koch W J. Targeting G.beta.gamma.signaling in arterial vascular smooth muscle proliferation: a novel strategy to limit restenosis. Proc Natl Acad Sci USA 1999;96:3945-50.). Thus, a combination of the (1), (3) and (4) polymorphisms are useful in the methods of the invention, and the "corresponding **combined genotypes** may be useful for the diagnosis of genetic risk for restenosis after balloon dilatation or in-stent restenosis." [0355]

The unpredictability of the art, the state of the prior art and level of skill in the art

According to the MPEP at 2164. 05(a), "(t)he state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains (and) the state of the art for a given technology is not static in time. It is entirely possible that a disclosure filed on January 2, 1990, would not have been enabled. However, if the same disclosure had been filed on January 2, 1996, it might have enabled the claims. Therefore, the state of the prior art must be evaluated for each application based on its filing date."

The Examiner alleges that "while the state of the art and level of skill in the art with regard to detection of a gene expression level is high, the level of unpredictability in associating any particular expression of a particular gene or combination of genes with a phenotype is even higher." (Office Action, p.10). The Examiner argues further that "the art teaches genetic variations and associations are often irreproducible" (Office Action, p.10). Applicants disagree.

The instant application provides polymorphisms, in particular polymorphisms (1) of the human apolipoprotein E gene, (3) of the human tumor necrosis factor α gene and (4) of the human G-protein β3 subunit gene that are shown in the Examples as being particularly effective to be used in determining genetic risk of restenosis after coronary angioplasty in an analysis of subjects who underwent balloon dilatation.

First, Applicants have provided teaching of clinical conditions that lead to the restenosis phenotype following coronary angioplasty. There is ample teaching in the art relating these clinical conditions to restenosis, for example as taught at paragraph [0002]:

> A number of clinical and angiographic findings, including hypertension, diabetes mellitus, hyperlipidemia, unstable angina, severe coronary artery stenosis and long stenosis lesions, have been reported to be associated with an increased risk of restenosis after coronary angioplasty (Hirshfeld J W Jr, Schwartz J S, Jugo R, et al. Restenosis after coronary angioplasty: a multivariate

statistical model to relate lesion and procedure variables to restenosis. The M-HEART Investigators. J Am Coll Cardiol 1991;18:647-56.; Weintraub W S, Kosinski A S, Brown C L 3rd, King S B 3rd. Can restenosis after coronary angioplasty be predicted from clinical variables? J Am Coll Cardiol 1993;21:6-14.; Stein B, Weintraub W S, Gebhart S P, et al. Influence of diabetes mellitus on early and late outcome after percutaneous transluminal coronary angioplasty. Circulation 1995;91:979-89.; Violaris A G, Melkert R, Serruys P W. Long-term luminal renarrowing after successful elective coronary angioplasty of total occlusions. A quantitative angiographic analysis. Circulation 1995;91:2140-50.).

Thus, given the knowledge in the art about clinical conditions that lead to the restenosis phenotype, one of skill in the art, knowing the clinical conditions associated with restenosis, would be able to correlate certain genes to the associated pathology.

Accordingly, in the instant invention the inventors have extracted 71 genes which were estimated to be associated with coronary arteriosclerosis, coronary artery spasm, hypertension, diabetes mellitus, hyperlipidemia, etc., and mainly selected 112 polymorphisms which were predicted to be associated with functional changes of genes by the use of a plurality of public databases. Then, as to 112 polymorphisms of 71 genes, association study with respect to myocardial infarction was carried out in 445 myocardial cases and 464 controls.

The Examiner relies on the references of Hirschhorn et al (Genetics in Medicine. Vol 4, No.2, p. 45 – 61, March 2002), Ioannidis (Nature Genetics, Vol. 29, p.306 – 309, November 2001), and Lucenti (The Scientist, 2004, 18(24): 20).

The Examiner argues that the Hirschhorn reference teaches "most reported (genetic) associations are not robust." (Office Action, p.10). The Hirschhorn reference is a review of genetic association studies; however Applicants point out that the Hirschhorn reference is from 2002. Moreover, in a 2003 report, the same author, Hirschhorn, teaches that meta-analysis of genetic association studies **supports a contribution of common variants to susceptibility to common disease** (Hirschhorn et al., Nature Genetics 33, 177 - 182 (2003)). The 2003 Hirschhorn reference "conclude(s) that there are probably

many common variants in the human genome with modest but real effects on common disease risk, and that studies using large samples will convincingly identify such variants." (Abstract; emphasis added).

The Examiner further cites the reference of Ioannidis and Lucentini to support his argument that "most gene association studies are typically wrong." The Ioannidis reference examines replication validity of genetic association studies. Ioannidis teaches that "the first study often suggests a stronger genetic effect than is found by subsequent studies. Both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism." (Abstract). The Examiner argues that the Lucentini reference teaches "that it is strikingly common for follow up studies to find gene-associations wrong." (Office Action, p.11). The Lucentini reference teaches that "'bigger sample sizes" and "revising statistical methods, should be included in the gene association studies." (Office Action, p.12).

First, the state of technology for examining gene expression has changed from the time of publication of the cited art. For example, use of microarrays and technology such as array comparative genomic hybridization that (CGH) provides detection of segmental DNA copy number alterations. CGH allows high-resolution examination for identifying genetic alterations and copy number variations on a genome-wide scale.

The instant invention provides reliable statistical analysis in a stepwise forward selection method of multivariate logistic regression, where either a dominant or recessive model is used based on the P values for association of each polymorphism with restenosis after coronary angioplasty, and an odds ratio is then determined.

Finally, the instant invention uses a large population size of 1869 subjects.

Taken together, the teachings of the specification and knowledge of one of skill in the art enables one of skill in the art to practice the full scope of the claimed invention without having to resort to undue experimentation. Applicants accordingly request that the

rejection be reconsidered and withdrawn.

Claim Rejections 35 U.S.C. §102(b)

Claim 1 has been rejected under 35 U.S.C. § 102(b) as being anticipated by Watanabe et al. (Thromb Haemost. 2001 Dec; 86(6): 1594-5).

Instant claim 1 has been cancelled making the rejection now moot.

Claim Rejections 35 U.S.C. §102(a)

Claim 1 has been rejected under 35 U.S.C. § 102(a) as being anticipated by Yamada et al. (Cited in IDS: Yamada et al. NEJM 2002 Dec 12; 347 (24): 1916 – 23).

Instant claim 1 has been cancelled making the rejection now moot.

In view of the above amendment and reply, Applicants believe the pending application is in condition for allowance.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105.

Dated: November 7, 2007

Respectfully submitted,

By _____

James E. Armstrong, IV
Registration No.: 42,266
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 239-0100
Attorneys/Agents For Applicant